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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	45

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/952,741	HATADA ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- Th MAILING DATE of this communication appears on the cov r sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Remand 2/9/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,12,13,15,16 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7, 12, 13, 15, 16 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/14/02*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4/5/04*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of Remand mailed on February 9, 2004, PROSECUTION IS HEREBY REOPENED. The grounds of rejections set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 2-7, 12, 13, 15, 16 and 20-24 are pending.

Information Disclosure Statement

The IDS filed November 14, 2002 listing the Nakajama et al. (1986) reference has been considered. A copy of the initialed and signed form PTO-1449 is attached hereto.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re*

Ockert, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 2, 5-7, 12 and 13 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-6 of U.S. Patent No. 6,638,748 issued on a division of the instant application. This is a double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4, 15, 16 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 3, with dependent claims 4, 15, 16, 20 and 21, is drawn to a DNA encoding an α–amylase having an amino acid sequence of SEQ ID NO:2 with one or more amino acids substituted, added, deleted or inserted and having the specific substrate specificity. Thus, the claim defines the amino acid sequence of α–amylase as different from SEQ ID NO:2 by at least one residue. However, because the number of amino acids encompassed by "more" is not limited, there is no limitation on the structural

homology with SEQ ID NO:2 or a DNA encoding thereof. Therefore, claim 3 is equivalent to a claim that is drawn to a DNA encoding α–amylase of an undefined structure. Such variant and a DNA encoding thereof encompass a great number of molecules, both naturally occurring and synthetic, encoding amino acid sequences some of which may not have any structural homology with SEQ ID NO: 2.

Thus, the claims recite an enormous genus of DNAs encoding variant alkaline liquefying α-amylases from any source characterized only by function and pH optimum.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these. Later, ENZO BIOCHEM, INC v. GEN-PROBE INCORPORATED (Fed. Cir. 2002) court adhered to Eli Lilly court by holding that the genus of nucleic acid sequences that hybridize under

highly stringent conditions are adequately described because "such conditions dictate that all species within a genus will be structurally similar". In contrast, in the instant case, there is no requirement for structural similarity. There is no adequate written description of the claimed genus because it does not distinguish the claimed genus from others, except by specific function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others such as other amylases. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of proteins the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

In the instant specification the genus of genus of DNAs encoding variant alkaline liquefying α-amylases from any source characterized only by function and pH optimum is represented by a single DNA that is a fragment of SEQ ID NO:1 encoding a deletion mutant of alkaline liquefying α-amylase having the sequence wherein 32 N-terminal amino acids of SEQ ID NO: 2 have been deleted (specification, paragraph bridging pages 11-12).

The specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being alkaline liquefying α-amylase with the specific substrate specificity and pH optimum at pH 8-9

and fails to provide any structure: specific function correlation present in all members of the claimed genus nor are they known in the art. Therefore, based on the instant disclosure, it is unpredictable which DNA will encode a mutant alkaline liquefying α-amylase with the desired properties.

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Claim 20 depends from claim 3 and limits the properties of the protein reciting "an isoelectric point higher than 8.5". Claim 21 depends from claim 3 and recites additional physico-chemical properties of an enzyme. Said properties are defined by broad ranges. DNAs encoding said variant amylases encompass a great number of molecules, both naturally occurring and synthetic.

The specification discloses only a single species of the claimed genus, the DNA encoding a N-terminal deletion mutant of SEQ ID NO: 2, *supra*.

The specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being alkaline liquefying α-amylase with the specific substrate specificity and pH optimum at pH 8-9 and fails to provide any correlation between the structural and recited physicochemical properties present in all members of the claimed genus nor it is known in the art. Furthermore, the recited physico-chemical properties are the properties of an enzyme not a DNA. Therefore, based on the instant disclosure, it is unpredictable which DNA will encode a mutant alkaline liquefying α-amylase with the desired properties.

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 22-24 are independent claims that are drawn to a DNA encoding alkaline liquefying α–amylase with pH optimum at pH 8-9 from any source comprising a DNA of 20-26 bp not all of which are defined. There is no recitation of any other properties of an enzyme. The DNA of the instant invention (SEQ ID NO:1) is 1776 bp long. Therefore, at most claims 22-24 recite 1.0-1.5% homology with SEQ ID NO:1. The recited structural feature of the genus (i.e., comprise a fragment of 20-26 nucleotides of SEQ ID NO:1) does not constitute a substantial portion of the genus as the remainder of the structure of a polypeptide with the requisite alkaline liquefying α-amylase activity is completely undefined. Fragments consisting of 20-26 nucleotides of SEQ ID NO:1 are highly unlikely to encode α-amylase activity and the specification does not define the remaining structural features necessary for members of the genus to be selected.

Thus, the claims recite an enormous genus of DNAs encoding alkaline liquefying α-amylases from any natural source which would include fungi, plants, animals, etc. as well man made amylases characterized only by function and pH optimum.

The specification discloses only two highly homologous species of the claimed genus, the DNAs encoding alkaline liquefying α-amylase of SEQ ID NO: 2 from *Bacillus* sp. KSM-AP1378 (SEQ ID NO:1) and its N-terminal deletion mutant, *supra*.

The specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being alkaline liquefying α-amylase with the specific substrate specificity and pH optimum at pH 8-9 and fails to provide any structure: specific function correlation present in all members of the claimed genus nor they are known in the art. Therefore, based on the instant disclosure, it is unpredictable which DNA will encode an alkaline liquefying α-amylase with the desired properties.

One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of proteins the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the amylases species within the genus from other amylases such that one can visualize or recognize the identity of the members of the genus.

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 3, 4, 15, 16 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA encoding an alkaline liquefying α–amylase having the amino acid sequence of SEQ ID NO:2 and its N-terminal deletion mutant that has a pH-optimum at pH 8-9 and the specific substrate

specificity, does not reasonably provide enablement for a DNA encoding an alkaline liquefying α–amylase having an amino acid sequence of SEQ ID NO:2 with one or more amino acids substituted, added, deleted or inserted and having the requisite properties or for a DNA encoding an α–amylase that has a pH-optimum at pH 8-9 and comprising a nucleotide fragment of about 20 bp. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible nucleic acid sequences encoding alkaline liquefying α–amylases having the specific desired characteristics.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature and breadth of the invention of claims 3, 4, 15, 16, 20 and 21 encompass any nucleic acid sequence encoding any mutant alkaline liquefying α-amylase having an amino acid sequence of SEQ ID NO:2 with one or more amino acids substituted, added, deleted or inserted and having the specific characteristics from any biological source, or derived by any type of mutation from SEQ ID NO: 2. This reads on

any structure without any structural limitations having an alkaline liquefying α–amylase activity with the requisite properties.

The nature and breadth of the invention of claims 22-24 encompass any nucleic acid sequence comprising a partial sequence of 20-26 nucleotides of SEQ ID NO:1 and encoding any naturally-occurring or mutant alkaline liquefying α–amylase having pH optimum at pH 8-9. The specific sequences recited in claims 22-24 represent less than 2% of the entire requisite DNA structure. Thus, with regard to the deficiency of structural limitations claims 22-24 are similar to claim 3. Therefore, one of skill in the art would have been required to make a structure that would impart the requisite properties (claims 3, 4, 15, 16, 20 and 21) or a structure that comprises a specific 20-26 nucleotide fragment and encodes an α-amylase with pH-optimum at pH 8-9 (claims 22-24).

The specification provides guidance and examples for obtaining DNAs encoding an alkaline liquefying α–amylase having an amino acid sequence of SEQ ID NO:2 from *Bacillus* sp. KSM-AP1378 and its N-terminal deletion mutant. While molecular biological techniques and genetic manipulation to make and use the claimed nucleic acid sequences are known in the prior art and the skill of the artisan are well developed, knowledge regarding the amino acid residues which are important to the enzymatic activity and folding of the α–amylase, the amino acid residues which can be inserted into or deleted from the amino acid sequence of SEQ ID NO: 2 without affecting the requisite specific enzymatic activity, amino acid homology among α–amylases with said specific enzymatic activity from various biological sources, and the nucleic acid

sequence homology among nucleic acid sequences encoding said α–amylases from various biological sources is lacking.

The prior art teaches the DNAs encoding alkaline liquefying α-amylases from *Bacillus* sp. #707 and *Bacillus licheniformis*, respectively (Tsukamoto et al. and Yuuki et al., respectively (form PTO-1449)). The DNAs disclosed by Tsukamoto et al. and Yuuki et al. encode the amino acid sequences which have about 87% and 69% identity to SEQ ID NO:2, respectively. However, the disclosed α–amylases have properties different from the α–amylase of the instant invention. In particular, said α–amylases do not have pH optimum at pH 8-9 (see, for example, Response under 37 CFR 1. 116 filed January 14, 2000, pages 7-8). Therefore, the prior art renders it highly unpredictable as to what amino acid residues can be modified in SEQ ID NO:2 without resulting in drastic changes in the properties of the enzyme.

The specification provides no guidance as to what amino acid residues are responsible for the requisite pH optimum and other specific properties imparted by SEQ ID NO:2 and therefore, what amino acid residues can be mutated without affecting the requisite properties.

Thus, searching for an alkaline liquefying α–amylase or a mutant thereof with desired characteristics is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a nucleic acid sequence encoding alkaline liquefying α–amylase with the requisite characteristics of unknown structure is enormous. Since routine experimentation in the art does not include screening vast numbers of genomic or cDNA

libraries constructed from large number of biological sources where the expectation of obtaining the desired α–amylase is unpredictable, one skilled in the art would require additional guidance, such as information regarding the biological source of the enzymes and their enzymatic properties and the amino acids which can be mutated without an adverse effect on the function and properties of the enzyme. Without such a guidance, the experimentation left to those skilled in the art is undue.

Response to Arguments

In the Reply Brief filed October 15, 2002 Applicants argue that "Appellants do not agree with the Examiner's assertion that the variants of the instant invention may not have any structural homology with SEQ ID NO:2. this may be the case if nothing were known about amylases. It appears to Appellants that the Examiner is examining the claim in a vacuum without taking into consideration what is known in the art about amylases" (Reply Brief, page 2). Applicants continue to describe four regions that are highly conserved in amylases referring the Nakajima et al. article (form PTO-1449 filed November 14, 2002). Applicants assert that "the skilled artisan is unlikely to change these parts of the protein" (page 3). This is not persuasive because the claims are no limited by the structure. While Nakajima et al. teach four conserved regions in amylases (Figure 1), only two regions were found in all 11 examined amylases (page 358). Each of the conserved regions comprises only a few amino acid residues. Neither Nakajima et al nor the specification teach residues corresponding to the conserved regions in SEQ ID NO:2. Nakajima et al. also teach that homology among amylases can be no

more than 10% (page 358). Furthermore, assuming that there are conserved regions in amylases, these regions are not responsible for the diverse properties of amylases. As discussed above, the alkaline liquefying α-amylases from *Bacillus* sp. #707 and *Bacillus licheniformis*, respectively have about 87% and 69% identity to SEQ ID NO:2, respectively. However, the disclosed α–amylases have properties different from the α–amylase of the instant invention. The specification fails to identify regions or residues that must be conserved in order for an alkaline liquefying α-amylase to retain the claimed requisite prosperities.

With regard to the enablement rejection, Applicants argue that "Appellants have also provided guidance in using the primers on the template DNA from Bacillus species. In the specification, please see the last paragraph on page 4, page 6, lines 6-10 and page 7, lines 1-12. Because these DNA primers were designed based on the highly conserved regions from the enzymes, the procedure elucidated in these paragraphs is a general procedure, which allows one to isolate other nucleic acids encoding variant proteins" (page 5). This is not persuasive because the specific primers based on SEQ ID NO:1 would allow to isolate highly homologous sequences from the sources where the highly homologous genes are known to be present. The primers must be highly specific in order to isolate the claimed genes and not the genes encoding α-amylases with different properties. The current claims encompass neither the template source nor the primers specific for the instant genes versus other homologous amylases. Applicants refer to Sambrook et al., pp.8.46-8.63 (attached as Exhibit A) to show that the techniques for "screening for clones that contain a cDNA of interest by

enzymological property (*i.e.*, ability to cleave glucosidic linkages) is well known in the art" (page 9). Applicants' arguments are not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., encoding an alkaline liquefying α-amylase with pH optimum 8-9 and specified substrate specificity) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

It is noted that Applicants submitted only pp.8.46-8.59 of Sambrook et al. as Appendix A.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

April 21, 2004

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